

Tetracyclines as an Oral Treatment Option for Patients with Community Onset Skin and Soft Tissue Infections Caused by Methicillin-Resistant *Staphylococcus aureus*[▽]

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Few data exist on the clinical utility of the expanded-spectrum tetracyclines doxycycline and minocycline for the treatment of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections (SSTI). We performed a retrospective cohort study of 276 patients who presented with 282 episodes of MRSA SSTI to the emergency room or outpatient clinic at two tertiary medical centers between October 2002 and February 2007. The median percentage of patients infected with MRSA strains that were susceptible to tetracycline was 95%. Time zero was defined as the time of the first incision and drainage procedure or, if none was performed, the time of the first positive wound culture. The median patient age was 48 years. Abscesses constituted the majority of clinical presentations (75%), followed by furuncles or carbuncles (13%) and cellulitis originating from a purulent focus of infection (12%). A total of 225 patients (80%) underwent incision and drainage. Doxycycline or minocycline was administered in 90 episodes (32%); the other 192 SSTI were treated with β -lactams. Treatment failure, defined as the need for a second incision and drainage procedure and/or admission to the hospital within at least 2 days after time zero, was diagnosed in 28 episodes (10%) at a median of 3 days after time zero. On logistic regression analysis, receipt of a β -lactam agent was the only clinical characteristic associated with treatment failure (adjusted odds ratio, 3.94; 95% confidence interval, 1.28 to 12.15; $P = 0.02$). The expanded-spectrum tetracyclines appear to be a reasonable oral treatment option for patients with community onset MRSA SSTI in areas where MRSA strains are susceptible to the tetracyclines.

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections acquired outside the health care setting have been increasingly reported worldwide (4, 10, 22, 32). Recent data suggest that these community-associated MRSA strains have replaced their methicillin-susceptible counterparts as the major cause of skin and soft tissue infections (SSTI) among patients who present to a clinic or emergency room in the United States (13, 19). The incision and drainage of pus collections constitute the most important aspects of the management of these infections (26). The additional role of antibiotic therapy for patients with suspected MRSA SSTI is less certain, as many SSTI episodes resolve with surgical drainage alone (10, 19, 24, 29, 33). Current guidelines suggest that alternative, non- β -lactam agents to which the organism is likely susceptible should be used in the empirical treatment of patients for whom antimicrobial therapy is deemed indicated (11, 26).

Potential treatment options for patients who do not require intravenous therapy include trimethoprim-sulfamethoxazole, clindamycin, and the tetracyclines (i.e., minocycline, doxycycline, and tetracycline). However, few data are currently available to guide clinicians in the optimal use of these agents. The expanded-spectrum tetracyclines doxycycline and minocycline demonstrate excellent oral bioavailability, tissue penetration,

and tolerability (14). Published reports on the use of these agents for the treatment of MRSA SSTI suggest their effectiveness but are limited to case studies (2, 3, 23). Thus, more data are needed. The primary objective of this study was to describe the clinical characteristics and outcomes of a large cohort of patients that received expanded-spectrum tetracyclines for tetracycline-susceptible MRSA SSTI acquired in an outpatient setting. As a secondary aim, we compared these patients to a patient cohort that shared very similar clinical characteristics but was treated with β -lactam monotherapy within the same time period.

MATERIALS AND METHODS

Setting. A retrospective cohort study of all patients who received monotherapy with either an expanded-spectrum tetracycline or a β -lactam for the treatment of community onset MRSA SSTI was conducted at the University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System between October 2002 and February 2007. The University of Arkansas for Medical Sciences Hospital serves as the only academic, tertiary-care referral center in the state; the Central Arkansas Veterans Healthcare System ranks among the largest institutions within the Veterans Affairs system.

Definition of terms and study design. A soft tissue infection was defined as having a community onset if the causative organism was isolated from a tissue specimen obtained in an outpatient setting or within 48 h of hospital admission. Patients with community onset MRSA SSTI were identified by review of the clinical microbiology laboratory records at both hospitals. An episode was further classified as a community-associated MRSA (CA-MRSA) SSTI if none of the following previously defined epidemiological criteria for a health care-associated infection were fulfilled: (i) prior history of an MRSA infection or colonization; (ii) the presence of an invasive device such as a central venous catheter; and (iii) dialysis, surgery, hospitalization, or residence in a long-term care facility in the 12 months preceding the culture (20).

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TABLE 1. Baseline demographic characteristics and comorbid conditions of patients with community onset^a MRSA SSTI treated with expanded-spectrum tetracyclines or β -lactams

Characteristic	Value for group treated with ^b :		OR (95% CI)	P
	Tetracycline (90 episodes)	β -Lactam (192 episodes)		
Age, yr [median (range)]	49 (22–85)	48 (18–82)		>0.2
Male gender	72 (80)	164 (85)	1.46 (0.76–2.82)	>0.2
Race			0.99 (0.60–1.64) ^c	>0.2 ^c
White	49 (54)	104 (54)		
Black	38 (42)	86 (45)		
Hispanic	3 (3)	2 (1)		
Previous β -lactam use ^d	31 (34)	71 (37)	1.12 (0.66–1.89)	>0.2
Previous fluoroquinolone use ^d	20 (22)	31 (16)	0.67 (0.36–1.26)	>0.2
CA-MRSA infection	62 (69)	131 (68)	0.97 (0.57–1.66)	>0.2
Intravenous drug use	2 (2)	10 (5)	2.42 (0.52–11.27)	>0.2
Hospital admission at time zero	9 (10)	36 (19)	2.08 (0.95–4.52)	0.06
Charlson score [median (range)] ^e	0 (0–6)	0 (0–6)		>0.2
Diabetes mellitus	19 (21)	28 (15)	0.64 (0.34–1.22)	0.17
Hepatitis C	13 (14)	20 (10)	0.69 (0.33–1.46)	>0.2
Coronary artery disease	8 (9)	16 (8)	0.93 (0.38–2.27)	>0.2
End-stage renal disease	0 (0)	0 (0)		
HIV/AIDS ^f	8 (9)	2 (1)	0.11 (0.02–0.52)	0.002
Current malignancy	3 (3)	3 (2)	0.46 (0.09–2.33)	>0.2
Chronic skin disease	2 (2)	7 (4)	1.67 (0.34–8.18)	>0.2
Peripheral vascular disease	5 (6)	5 (3)	0.46 (0.13–1.61)	>0.2

^a The SSTI was considered to have a community onset if the organism was isolated from a culture specimen obtained in an outpatient setting or within 48 h after admission.

^b Data are numbers (percentages) of patients exhibiting the characteristic, unless otherwise indicated.

^c For white versus nonwhite.

^d Within the previous 12 months. The use was unrelated to the current SSTI episode.

^e Assigned as described previously in reference 5.

^f HIV, human immunodeficiency virus.

SSTI episodes were grouped into three categories: (i) primary cellulitis which extended from a visible focus of infection, such as folliculitis, a minor abscess, or a nonchronic skin ulcer; (ii) furuncles or carbuncles; and (iii) cutaneous abscesses. Minor infections, such as impetigo and folliculitis, which generally require no or only topical antibiotic therapy, were excluded, as were complicated infections that involved deep structures, such as tendons, fascia, and muscle, as demonstrated by operative or radiological findings. Postoperative wound infections and chronic processes, including diabetic foot infections and nonhealing skin ulcers, were also excluded, as were cases in which multiple organisms were isolated from a wound culture.

The time zero of the study was defined as the day of the first incision and drainage procedure. For those patients on whom surgical drainage was not performed, the date of the first positive culture from a wound exudate, needle aspirate, or skin biopsy specimen was designated time zero. Treatment failure was the primary outcome of interest and was defined by the presence of two criteria: (i) documented worsening of clinical signs and symptoms of infection, such as increased purulence, erythema, induration, and/or tenderness at least 2 days after time zero, and (ii) the performance of a second, not previously planned incision and drainage procedure and/or admission to the hospital, both by at least 2 days after time zero.

Doxycycline and minocycline were both given orally at a dose of 100 mg twice daily. β -Lactam therapy consisted of intravenous agents such as cefazolin or piperacillin-tazobactam and oral agents such as cephalexin, dicloxacillin, or amoxicillin-clavulanate administered in standard doses to the majority of patients. Patients without signs of treatment failure who had received at least 3 days of β -lactam monotherapy and whose therapy was subsequently changed to another agent (in response to results from antimicrobial susceptibility testing in the majority of cases) were included as β -lactam treatment successes.

The study was approved by the institutional review boards of both hospitals.

Data review. The inpatient, outpatient, emergency department, and pharmacy records of all patients with MRSA cultured from a normally nonsterile site within the observation period were reviewed to ensure enrollment of all episodes that fulfilled our inclusion criteria. Sociodemographic and clinical data were obtained with the use of a standardized data extraction instrument. For abscesses, furuncles, and carbuncles, the largest diameter of the lesion was recorded. Comorbidity was assessed with the Charlson comorbidity score (5, 17). The systemic inflammatory response syndrome (SIRS) was diagnosed based on previously

described criteria (1). We also determined whether the incision and drainage procedure at time zero was performed by a surgical service or a nonsurgical service, including the emergency medicine department. Patient follow-up was recorded as the number of clinical encounters that occurred between days 2 and 21 after time zero. If a patient experienced more than one eligible SSTI episode during the observation period, the later episode was included as an independent event if it occurred at least 1 month after the first presentation and involved a different body site.

Microbiological methods. The *Staphylococcus aureus* isolates' susceptibilities to oxacillin, tetracycline, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin, rifampin, and vancomycin were determined by the broth microdilution method with the Vitek 2 system (bioMérieux, Durham, NC). The double-disk diffusion assay was performed to test for inducible clindamycin resistance in accordance with the recommendations of the Clinical and Laboratory Standards Institute (6, 7).

Statistical analysis. Bivariate analyses were conducted by Pearson's χ^2 test, Fisher's exact test, and the Wilcoxon rank sum test to compare categorical and continuous (but not normally distributed) variables ($P < 0.05$). We calculated odds ratios (ORs) in order to facilitate comparison to the results from multivariate analyses. Logistic regression analyses that included interaction terms were conducted to derive independent risk factors for treatment failure. Factors with a P value of <0.2 on bivariate analysis were included in the model. SPSS for Windows software, version 11.0 (SPSS), was used for all statistical analyses.

RESULTS

MRSA was isolated from a total of 4,621 clinical specimens during the study period. A total of 319 community onset MRSA SSTI episodes that fulfilled our screening criteria were identified. Of these, a total of 37 episodes were excluded for the following reasons: patients did not return for a scheduled follow-up appointment ($n = 28$), patients received only 1 or 2 days of β -lactam therapy and were therefore considered unevaluable ($n = 6$), medical records were incomplete ($n = 2$), or

TABLE 2. Clinical characteristics of and outcomes for patients with community onset^a MRSA SSTI treated with expanded-spectrum tetracyclines or β -lactams

Characteristic	Value for group treated with ^b :		OR (95% CI)	P
	Tetracycline (90 episodes)	β -Lactam (192 episodes)		
Type of infection			1.12 (0.63–1.99)	>0.2 ^c
Abscess	66 (73)	145 (76)		
Cellulitis	9 (10)	26 (14)		
Furuncle/carbuncle	15 (17)	21 (11)		
Lesion size, cm [median (interquartile range)] (<i>n</i> = 206) ^d	4 (3–6)	4 (3–5)		>0.2
SIRS (<i>n</i> = 249)	13 (17)	28 (16)	0.98 (0.48–2.01)	>0.2
Incision and drainage performed at time zero	69 (77)	156 (81)	1.32 (0.72–2.42)	>0.2
Incision and drainage performed by a surgical service (<i>n</i> = 225)	31 (45)	100 (64)	2.19 (1.23–3.90)	0.01
Site of infection:				
Head and neck	8 (9)	13 (7)	0.74 (0.30–1.87)	>0.2
Upper extremity ^e	19 (21)	40 (21)	0.98 (0.53–1.82)	>0.2
Trunk	13 (14)	21 (11)	0.73 (0.35–1.53)	>0.2
Genitoperineal/perirectal	9 (10)	12 (6)	0.60 (0.24–1.48)	>0.2
Lower extremity ^f	33 (37)	78 (41)	1.18 (0.71–1.98)	>0.2
Hand or foot	8 (9)	28 (15)	1.75 (0.76–4.01)	0.18
Treatment failure	4 (4)	24 (13)	3.07 (1.03–9.14)	0.035
Repeat incision and drainage performed ^g	4 (100)	19 (79)		
Subsequent hospital admission		16 (67)		
Median no. of follow-up visits (range)	1 (1–4)	1 (1–5)		0.18

^a The SSTI was considered to have a community onset if the organism was isolated from a culture specimen obtained in an outpatient setting or within 48 h after admission.

^b Data are numbers (percentages) of patients exhibiting the characteristic, unless otherwise indicated.

^c For abscess versus nonabscess.

^d Maximum diameters of abscesses, furuncles, and carbuncles.

^e Including the axilla but not including the hand.

^f Including buttocks but not including feet.

^g Refers to the subset of patients whose sites of SSTI were incised and drained (*n* = 225).

concomitant blood cultures grew MRSA (*n* = 1). Excluded patients did not differ significantly from the final cohort with regard to gender, type of infection, presence of SIRS, surgical drainage, and type of antimicrobial therapy (*P* > 0.1). The final cohort consisted of 276 patients with 282 independent episodes of community onset MRSA SSTI. Four patients experienced two episodes and one patient experienced three independent episodes during the study period. All data presented hereinafter refer to the total number of 282 SSTI episodes. A total of 90 episodes (32%) were treated with expanded-spectrum-tetracycline monotherapy, whereas the other 192 episodes (68%) were treated with β -lactam agents. At our hospitals, the rates of susceptibility of MRSA strains to the tetracyclines remained stable at 95% (range, 94% to 96% per year) throughout the 53-month observation period (*P* was >0.2 for the trend).

Baseline demographics and comorbidities. The two treatment groups were similar with regard to baseline demographic characteristics and comorbidities (Table 1). For the entire cohort (282 episodes), the median patient age was 48 years and 236 patients (84%) were male. A total of 184 SSTI episodes (65%) were treated at the Central Arkansas Veterans Healthcare System. Twelve patients (4%) used intravenous drugs. The administration of antibiotics within the 12 months prior to presentation was common; β -lactams (36%) and fluoroquinolones (18%) were the most commonly prescribed agents. One hundred ninety-three episodes (68%) fulfilled the criteria of a CA-MRSA SSTI. The levels of susceptibility to non- β -lactam antibiotic classes were 5% for macrolides (13 of 282 isolates), 71% for ciprofloxacin (199 of 279 isolates tested), 99.5% for

trimethoprim-sulfamethoxazole (217 of 218 isolates tested), 100% for rifampin and gentamicin (219 isolates tested, each), 100% for vancomycin (all 282 isolates tested), and 99% for clindamycin (278 of 282 isolates tested). The double-disk diffusion test was performed routinely only toward the end of the study period; only 1 (3%) of 32 tested isolates displayed inducible clindamycin resistance.

Overall, our cohort was relatively healthy, as indicated by a median Charlson score of 0; a score of 4 or higher was noted for only seven subjects (2%). Diabetes mellitus, hepatitis C, and coronary artery disease were the most common comorbidities. Human immunodeficiency virus/AIDS was more frequently observed in the expanded-spectrum-tetracycline group, but the overall prevalence was low (4%).

Clinical presentation and therapy. Table 2 describes the clinical characteristics and patient outcomes categorized by type of antimicrobial therapy. For the entire cohort (282 episodes of SSTI), abscesses were the most commonly encountered entity (75%). Only 35 (12%) of the 282 episodes were classified as cellulitis which originated from a purulent focus of infection. The maximum diameter of induration was documented for 206 (86%) of 247 abscesses, furuncles, or carbuncles; the median lesion size was 4 cm (interquartile range, 3 to 5 cm), and diameters did not differ significantly between the two treatment groups. A second pathogen grew in four clinical specimens; a group B streptococcus, *Proteus vulgaris*, a coagulase-negative staphylococcus, and a viridans group streptococcus were present in one clinical specimen each. A surgical drainage procedure was performed on the majority of patients

TABLE 3. Association of demographic and clinical characteristics with treatment failure in patients with community onset^a MRSA SSTI

Characteristic	Value for group that had ^b :		OR (95% CI)	P
	Treatment success (254 episodes)	Treatment failure (28 episodes)		
Age, yr [median (range)]	48 (18–85)	43 (22–59)		0.06
Male gender	211 (83)	25 (89)	1.70 (0.49–5.88)	>0.2
White race	138 (54)	15 (54)	0.97 (0.44–2.12)	>0.2
Previous β -lactam use ^c	93 (37)	9 (32)	0.82 (0.36–1.89)	>0.2
CA-MRSA infection	174 (69)	19 (68)	0.97 (0.42–2.24)	>0.2
Intravenous drug use	10 (4)	2 (7)	1.88 (0.39–9.03)	>0.2
Hospital admission at time zero	41 (16)	4 (14)	0.87 (0.29–2.63)	>0.2
Charlson score [median (range)] ^d	0 (0–6)	0 (0–4)		>0.2
Diabetes mellitus	43 (17)	4 (14)	0.82 (0.27–2.48)	>0.2
Hepatitis C	29 (11)	4 (14)	1.29 (0.42–3.99)	>0.2
HIV/AIDS ^e	8 (3)	2 (7)	2.37 (0.48–11.73)	>0.2
Peripheral vascular disease	9 (4)	1 (4)	1.01 (0.12–8.27)	>0.2
Type of infection:				
Abscess	189 (74)	22 (79)	1.26 (0.49–3.25)	>0.2
Furuncle/carbuncle	34 (13)	2 (7)	0.50 (0.11–2.19)	>0.2
Cellulitis	31 (12)	4 (14)	1.20 (0.39–3.69)	>0.2
Lesion size, cm [median (interquartile range)]	4 (3–5)	4 (3–6)		>0.2
(<i>n</i> = 206) ^f				
SIRS (<i>n</i> = 249)	36 (16)	5 (19)	1.24 (0.44–3.49)	>0.2
Incision and drainage performed by surgical service (<i>n</i> = 225) ^g	120 (60)	11 (44)	0.52 (0.23–1.21)	0.13
Hand or foot location site	33 (13)	3 (11)	0.80 (0.23–2.81)	>0.2
β -Lactam therapy	168 (66)	24 (86)	3.07 (1.03–9.14)	0.035

^a The SSTI was considered to have a community onset if the organism was isolated from a culture specimen obtained in an outpatient setting or within 48 h after admission.

^b Data are numbers (percentages) of patients exhibiting the characteristic, unless otherwise indicated.

^c Within the previous 12 months. The use was unrelated to the current SSTI episode.

^d Assigned as described previously in reference 5.

^e HIV, human immunodeficiency virus.

^f Maximum diameters of abscesses, furuncles, and carbuncles.

^g Relative to a subset of the entire cohort as defined in Materials and Methods.

in both treatment groups. One hundred ninety-three (91%) of 211 abscesses required incision and drainage. Of note, most patients with cellulitis (66%) also underwent incision and drainage of the primary focus of infection. Needle aspiration of abscess fluid, manual expression of pus, or spontaneous wound drainage was considered adequate in the 57 episodes (20%) managed without formal incision and drainage.

Within the expanded-spectrum-tetracycline-treated cohort (*n* = 90), doxycycline was administered for 87 episodes (97%) and minocycline for 3 episodes (3%), for a median duration of 10 days (range, 3 to 20 days). Within the β -lactam-treated cohort, oral cephalexin (*n* = 131) and amoxicillin-clavulanate (*n* = 48) were the most commonly prescribed agents. Eighty-six (96%) of 90 patients treated with an expanded-spectrum tetracycline had a successful outcome compared to 168 (88%) of 192 patients who received β -lactam monotherapy (*P* was 0.035 on bivariate analysis). Of note, the group of 168 β -lactam treatment successes included 20 episodes (12%) for which treatment was changed from a β -lactam to an active agent after a median of 4 days (range, 3 to 6 days), based on available antimicrobial susceptibility data. As these episodes did not fulfill our criteria for treatment failure, they were included as β -lactam treatment successes in our analyses.

Clinical outcome and predictors of treatment failure. Treatment failure occurred for 28 (10%) of 282 episodes at a median of 3 days (range, 2 to 21 days; interquartile range, 2 to 3 days) after time zero. The majority of clinical failures (23 of 28) consisted of patients who required a repeat incision and drain-

age procedure due to worsening clinical findings on a follow-up visit, with or without concomitant hospital admission. The other five patients required subsequent hospital admission due to failing antibiotic therapy and improved after treatment with an active agent (an agent to which the organism demonstrated in vitro susceptibility) and additional wound care were initiated.

Table 3 shows predictors of treatment failure on bivariate analyses. A variety of clinical parameters, such as the severity of an underlying illness, the presence of a SIRS, or the site of infection, were not associated with a negative outcome. After adjustment for potential confounders on logistic regression analysis, receipt of a β -lactam agent remained the only clinical predictor of treatment failure (adjusted OR, 3.94; 95% confidence interval [CI], 1.28 to 12.15; *P* = 0.02).

Our study design did not allow us to determine the direct impact of surgical drainage on patient outcome. Therefore, we performed a subgroup analysis that included only patients who underwent incision and drainage at time zero (*n* = 225). β -Lactam therapy remained significantly associated with a negative outcome in this more strictly defined subgroup (adjusted OR, 3.39; 95% CI, 1.07 to 10.75; *P* = 0.04).

DISCUSSION

Current guidelines for the management of staphylococcal SSTI emphasize the importance of surgical drainage of focal pus collections (26). With regard to adjunctive antimicrobial

therapy, expanded-spectrum tetracyclines are considered potential treatment alternatives for patients with less-serious MRSA SSTI that do not require intravenous therapy (11). However, only a few data are available on the use of these agents for this indication. To our knowledge, we have performed the largest study to date that investigates the outcomes of patients with community onset, tetracycline-susceptible MRSA SSTI treated with expanded-spectrum tetracyclines. Eighty-six (96%) of 90 episodes, of which the majority were abscesses, were treated successfully; four patients required a repeat incision and drainage procedure and subsequently improved on continued tetracycline therapy.

Older studies found minocycline to have a more-potent *in vitro* antistaphylococcal activity than doxycycline (16, 18). Minocycline was also used successfully in a few reported cases of serious infections, such as endocarditis or osteomyelitis (15, 34). These data on its clinical utility are supported by results from a rabbit endocarditis model that used a single MRSA strain (21). In this study, reductions of the bacterial density of the vegetation were similar among vancomycin- and minocycline-treated animals, combined with better tissue penetration by the latter agent. In our study, the vast majority of patients (97%) received doxycycline monotherapy. Therefore, we were not able to compare its therapeutic efficacy to that of minocycline. Both agents were well tolerated; mild gastrointestinal side effects or a rash occurred in three patients, but these symptoms did not necessitate a modification from doxycycline therapy to a different agent.

At our institutions, the rates of susceptibility to the tetracyclines among MRSA isolates have remained high and stable at approximately 95% over the last 4 years. This number includes nosocomial isolates that generally tend to be less susceptible (20). During our 53-month observation period, patients experiencing eight episodes of tetracycline-resistant MRSA SSTI not enrolled in this study were treated with a tetracycline; one (13%) failed treatment. *Staphylococcus aureus* resistance to the tetracyclines is frequently conferred by the chromosomally located Tet M determinant, which mediates protective modifications on the ribosome; its presence generally renders all class members, including minocycline, ineffective (25, 28). However, some MRSA strains that display resistance to tetracycline contain only the Tet K determinant, coding for drug efflux; the growth of these isolates is still inhibited by minocycline. Because commonly used clinical microbiology laboratory methodologies are not capable of differentiating these genotypes, clinicians should consider all isolates that display nonsusceptibility to tetracycline to be resistant to minocycline also (31). A recent large study that enrolled patients with acute, purulent SSTI from 11 urban emergency departments in the United States described results similar to ours: 207 (92%) of 226 MRSA isolates were susceptible to the tetracyclines (19). Clinicians who consider prescribing an expanded-spectrum tetracycline for the treatment of a suspected MRSA SSTI should be familiar with their local rates of resistance, as these rates vary within North America and worldwide (8, 10, 12). This drug class may be especially useful in patients with a sulfonamide allergy, an entity diagnosed for about 5% of patients in a large general-practice database (27).

The importance of the pulsed-field-type USA300 MRSA strain as the most common cause of community-associated

SSTI in the United States has recently been documented (19). This strain displays previously described molecular characteristics, such as the presence of a specific mobile gene complex that confers methicillin resistance (SCC*mecA* type IV) and the Panton-Valentine leukocidin (30). Pulsed-field gel electrophoresis data were not available in our study; instead, we used the epidemiological definition of a community onset infection as supported by previous reports (13, 20). However, a recent study performed by the Arkansas Department of Health also demonstrated USA300 to be the most frequently isolated strain from staphylococcal SSTI in central Arkansas (24). Furthermore, antimicrobial susceptibility patterns to non- β -lactam agents such as the fluoroquinolones or trimethoprim-sulfamethoxazole in our cohort were very similar to those observed in other studies (9, 13). Thus, we conclude that the microbiological and patient characteristics in our study may be applicable to other geographical regions.

As a second objective of our study, we compared the 90 patients treated with expanded-spectrum-tetracycline monotherapy to a group of 192 subjects who received β -lactams. Both cohorts were very similar with regard to a variety of underlying demographic and clinical characteristics, including surgical wound drainage at time zero. β -Lactam use was associated with a higher rate of treatment failure than was expanded-spectrum-tetracycline use (12.5% versus 4.4%) and remained a significant predictor of a negative outcome on logistic regression analysis ($P = 0.02$). Interpreted differently, 13 patients would have to be treated with expanded-spectrum tetracyclines in order to prevent one additional treatment failure associated with inactive antistaphylococcal therapy. Therefore, our results support the recommendations of current guidelines that emphasize the primary importance of surgical drainage, which may then be followed by the administration of agents that are active against methicillin-resistant staphylococcal isolates. More data are needed to determine which patients would benefit most from adjunctive antimicrobial therapy.

Our study has disadvantages in addition to those already mentioned. Patients were not randomly assigned to either type of antimicrobial therapy. Thus, our results may have been influenced by differences between the two groups that were not accounted for in the analysis. However, the high degree of similarity with regard to a variety of important clinical characteristics, such as underlying disease, clinical presentation, and rates of surgical drainage, among both treatment groups makes this less likely. Additionally, the difference in outcome between the two subgroups may have been overestimated by the exclusion of a number of patients who did not present for follow-up, presumably due to treatment success not requiring a second visit. The relatively small number of excluded patients limits this possibility. Furthermore, the retrospective design may have introduced additional forms of bias, such as misclassification and outcome bias, which we attempted to limit by the use of clear and objective definitions of the main study parameters, such as time zero and treatment outcome.

In summary, the expanded-spectrum tetracyclines appear to be a promising treatment option for patients who present with a suspected CA-MRSA SSTI that does not require intravenous therapy. Current local antimicrobial resistance patterns should be taken into account in therapeutic decision making. Studies that compare the efficacies of these agents to those of other

treatment options for CA-MRSA SSTI, such as clindamycin, linezolid, or the sulfonamides, are needed to guide clinicians in the management of this emerging clinical entity.

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REFERENCES

- American College of Chest Physicians, Society of Critical Care Medicine Consensus Conference Committee. 1992. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit. Care Med.* **20**:864–874.
- Barnes, E. V., D. P. Dooley, M. J. Hepburn, and S. E. Baum. 2006. Outcomes of community-acquired, methicillin-resistant *Staphylococcus aureus*, soft tissue infections treated with antibiotics other than vancomycin. *Mil. Med.* **171**:504–507.
- Carter, M. K., V. A. Ebers, B. K. Younes, and M. K. Lacy. 2006. Doxycycline for community-associated methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections. *Ann. Pharmacother.* **40**:1693–1695.
- Ceccarelli, D., J. Mondlane, M. Sale, A. M. Salvia, E. Folgosa, P. Cappuccinelli, and M. M. Colombo. 2005. Sporadic methicillin resistance in community acquired *Staphylococcus aureus* in Mozambique. *New Microbiol.* **28**:327–336.
- Charlson, M. E., P. Pompei, K. L. Ales, and C. R. MacKenzie. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* **40**:373–383.
- Clinical and Laboratory Standards Institute. 2006. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th ed. Approved standard M7-A7. Clinical and Laboratory Standards Institute, Wayne, PA.
- Clinical and Laboratory Standards Institute. 2006. Performance standards for antimicrobial susceptibility testing. Sixteenth informational supplement M100-S16. Clinical and Laboratory Standards Institute, Wayne, PA.
- Diekema, D. J., M. A. Pfaller, F. J. Schmitz, J. Smayevsky, J. Bell, R. N. Jones, and M. Beach. 2001. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. *Clin. Infect. Dis.* **32**:S114–S132.
- Diep, B. A., H. A. Carleton, R. F. Chang, G. F. Sensabaugh, and F. Perdreau-Remington. 2006. Roles of 34 virulence genes in the evolution of hospital- and community-associated strains of methicillin-resistant *Staphylococcus aureus*. *J. Infect. Dis.* **193**:1495–1503.
- Fridkin, S. K., J. C. Hageman, M. Morrison, L. T. Sanza, K. Como-Sabetti, J. A. Jernigan, K. Harriman, L. H. Harrison, R. Lynfield, and M. M. Farley. 2005. Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N. Engl. J. Med.* **352**:1436–1444.
- Grayson, M. L. 2006. The treatment triangle for staphylococcal infections. *N. Engl. J. Med.* **355**:724–727.
- Han, L. L., L. K. McDougal, R. J. Gorwitz, K. H. Mayer, J. B. Patel, J. M. Sennott, and J. L. Fontana. 2007. High frequencies of clindamycin and tetracycline resistance in methicillin-resistant *Staphylococcus aureus* pulsed-field type USA300 isolates collected at a Boston ambulatory health center. *J. Clin. Microbiol.* **45**:1350–1352.
- King, M. D., B. J. Humphrey, Y. F. Wang, E. V. Kourbatova, S. M. Ray, and H. M. Blumberg. 2006. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. *Ann. Intern. Med.* **144**:309–317.
- Klein, N. C., and B. A. Cunha. 1995. Tetracyclines. *Med. Clin. N. Am.* **79**:789–801.
- Lawlor, M. T., M. C. Sullivan, R. E. Levitz, R. Quintiliani, and C. Nightingale. 1990. Treatment of prosthetic valve endocarditis due to methicillin-resistant *Staphylococcus aureus* with minocycline. *J. Infect. Dis.* **161**:812–814.
- Leigh, D. A., and K. Simmons. 1974. Effect of minocycline on tetracycline-resistant *Staphylococcus aureus*. *Lancet* **i**:1006.
- Lesens, O., C. Methlin, Y. Hansmann, V. Remy, M. Martinot, C. Bergin, P. Meyer, and D. Christmann. 2003. Role of comorbidity in mortality related to *Staphylococcus aureus* bacteremia: a prospective study using the Charlson weighted index of comorbidity. *Infect. Control Hosp. Epidemiol.* **24**:890–896.
- Minuth, J. N., T. M. Holmes, and D. M. Musher. 1974. Activity of tetracycline, doxycycline, and minocycline against methicillin-susceptible and -resistant staphylococci. *Antimicrob. Agents Chemother.* **6**:411–414.
- Moran, G. J., A. Krishnadasan, R. J. Gorwitz, G. E. Fosheim, L. K. McDougal, R. B. Carey, and D. A. Talan. 2006. Methicillin-resistant *Staphylococcus aureus* infections among patients in the emergency department. *N. Engl. J. Med.* **355**:666–674.
- Naimi, T. S., K. H. LeDell, K. Como-Sabetti, S. M. Borchardt, D. J. Boxrud, J. Etienne, S. K. Johnson, F. Vandenesch, S. Fridkin, C. O'Boyle, R. N. Danila, and R. Lynfield. 2003. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* **290**:2976–2984.
- Nicolau, D. P., C. D. Freeman, C. H. Nightingale, C. J. Coe, and R. Quintiliani. 1994. Minocycline versus vancomycin for treatment of experimental endocarditis caused by oxacillin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* **38**:1515–1518.
- Piao, C., T. Karasawa, K. Totsuka, T. Uchiyama, and K. Kikuchi. 2005. Prospective surveillance of community-onset and healthcare-associated methicillin-resistant *Staphylococcus aureus* isolated from a university-affiliated hospital in Japan. *Microbiol. Immunol.* **49**:959–970.
- Ruhe, J. J., T. Monson, R. W. Bradsher, and A. Menon. 2005. Use of long-acting tetracyclines for methicillin-resistant *Staphylococcus aureus* infections: case series and review of the literature. *Clin. Infect. Dis.* **40**:1429–1434.
- Ruhe, J. J., N. Smith, R. W. Bradsher, and A. Menon. 2007. Community-onset methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections: impact of antimicrobial therapy on outcome. *Clin. Infect. Dis.* **44**:777–784.
- Schmitz, F. J., A. Krey, R. Sadurski, J. Verhoef, D. Milatovic, and A. C. Fluit. 2001. Resistance to tetracycline and distribution of tetracycline resistance genes in European *Staphylococcus aureus* isolates. *J. Antimicrob. Chemother.* **47**:239–240.
- Stevens, D. L., A. L. Bisno, H. F. Chambers, E. D. Everett, P. Dellinger, E. J. Goldstein, S. L. Gorbach, J. V. Hirschmann, E. L. Kaplan, J. G. Montoya, and J. C. Wade. 2005. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin. Infect. Dis.* **41**:1373–1406.
- Strom, B. L., R. Schinnar, A. J. Apter, D. J. Margolis, E. Lautenbach, S. Hennessy, W. B. Bilker, and D. Pettitt. 2003. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N. Engl. J. Med.* **349**:1628–1635.
- Strommenger, B., C. Kettlitz, G. Werner, and W. Witte. 2003. Multiplex PCR assay for simultaneous detection of nine clinically relevant antibiotic resistance genes in *Staphylococcus aureus*. *J. Clin. Microbiol.* **41**:4089–4094.
- Szumowski, J. D., D. E. Cohen, F. Kanaya, and K. H. Mayer. 2007. Treatment and outcomes of infections by methicillin-resistant *Staphylococcus aureus* at an ambulatory clinic. *Antimicrob. Agents Chemother.* **51**:423–428.
- Tenover, F. C., L. K. McDougal, R. V. Goering, G. Killgore, S. J. Projan, J. B. Patel, and P. M. Dunman. 2006. Characterization of a strain of community-associated methicillin-resistant *Staphylococcus aureus* widely disseminated in the United States. *J. Clin. Microbiol.* **44**:108–118.
- Trzcinski, K., B. S. Cooper, W. Hryniewicz, and C. G. Dowson. 2000. Expression of resistance to tetracyclines in strains of methicillin-resistant *Staphylococcus aureus*. *J. Antimicrob. Chemother.* **45**:763–770.
- Witte, W., C. Bräulke, C. Cuny, B. Strommenger, G. Werner, D. Heuck, U. Jappe, C. Wendt, H. J. Linde, and D. Harmsen. 2005. Emergence of methicillin-resistant *Staphylococcus aureus* with Panton-Valentine leukocidin genes in central Europe. *Eur. J. Clin. Microbiol. Infect. Dis.* **24**:1–5.
- Young, D. M., H. W. Harris, E. D. Charlebois, H. Chambers, A. Campbell, F. Perdreau-Remington, C. Lee, M. Mankani, R. Mackersie, and W. P. Schecter. 2004. An epidemic of methicillin-resistant *Staphylococcus aureus* soft tissue infections among medically underserved patients. *Arch. Surg.* **139**:947–951.
- Yuk, J. H., M. C. Dignani, R. L. Harris, M. W. Bradshaw, and T. W. Williams. 1991. Minocycline as an alternative antistaphylococcal agent. *Rev. Infect. Dis.* **13**:1023–1024.